# This Page Is Inserted by IFW Operations and is not a part of the Official Record

# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.

ুত্র প্রথমিত ব European Patent Office

(19)

Description

rd Deutima Viscous and stight

#### **TECHNICAL FIELD**

DISCLOS - JETHERWENTON

. 'n' "ules or tablets; ' ::

e capsule size y adult patients

· ficult to take: Inc.

ingly are large-

GLAGAR DE MOST

opression to

ginor summigrati

's ducing the

pon.its:beingau

ᢊ 🔝 to provide

This invention relates to β-lactam antibiotic-containing tablets and a method of producing the same. More particularly, it relates to tablets of the above variety which can be orally taken either as such or, in taking by, for example ithe its aged who have difficulties in swallowing eas a dispersion available upon dropping the same into water in a glass for self. To James General officers and, as a result, the inventor invented Membranes entigory proportion bottom; and to an entire or the second of the control of the co how good celf-disintegrating pincurates and can be produced by a conventional method. Further more, the inventor round that when granulation is performed using attained is ADD/JOHHDATARING REPARCED.

refugion of actioned ensepropyl alcohol, facilities anowing befrer dispersibility upon self-lisability, afron can be obtained. Racticularly in Europe, and America, where β-Jactam antibiotics such as ections and configurate administered gen-have to be considerably large in size. When 400 mg potrarcy caps reaches approximately. No. 0, so that not only patients have become reluctant to take them or get a repulsive sons the case of tablets, too 400 mg potency training

racus binder spronelly together with one. besie The problems encounter disetaking -patientsion.the a sin ur ~ theme?"

Theref: tablet size at ! a dosage to: simply dropped .... of advanced age u

duricu. Is in swallowing the dosage form as such. The expression "rapid self-disinis that when the preparation is dropped into a glass containing a liquid such as water, tegration" as used he. 🦠 the tablet form spontaneo. .....; collapses generally within 3 minutes, preferably within 1 minute, so that said preparation can be orally taken in disperuing form without awaiting long before taking. It is indeed easy to produce hables capable of sent-disintegrating very rapidly by incorporating an effervescent

agent comprising a combination of sodium hydrogen carbonate and tartaric acid, for instance. However, when such tablets are orally taken, they give off bubbles in the oral cavity, so that patients feel a discoinfort or an unnecessary sensation of anxiety. For securing a good shelf-life in a humid environment, it is necessary to use a moisture-proof packaging waping the dosage form which the present invention is material, which increases the production cost. Therefore, mulation enabling very rapid self-disintegration without intended to provide, it has been a tough problem to find the aid of any effervescent component.

For producing 8-lactam antibiotic-containing table in the form of a dispersion resulting from self-dicir 0281200 B (corresponding Japanese patent ar to 70% by weight, based on the weight a first disintegrator and 2 to 20% h a second disintegrator.

However, said first disinte tion of a binder component stantially nil. This is becage process for producing is employed which co tured it it is a side of a ... are formed inevitably & , for tableting of is a pac-

Meanwhile table name of Fisinoxin S been granted: Saich Land herice is vere largerar e Moc 'phatitute conf orally taken, give a bit. it thus becomesmee.... tion levels and thus suited for tal is a problemes ideamantely the way.

be easily ingested as they are and be also ingested a technology is described in European Patent EP Koho S63-301820), which comprises adding 24 crystalline cellulose or microfine cellulose as tuted hydroxypropylcellulose or the like as

from rapid suff disinles.

tablet size. In addition, the proporon the antibiotic, hence is subsintegrating properties. In the an integrity of the artefact se and kneading the mixe a resulto large lumps on to provide granules. mito author e an

> incien the trailing an patent has: bout: 970 my isabib bil.. DI REGINARIA C-laised ˈdi-

injuriare my dayou wever, where com....

os. ties of talliets become power warsy

. FARET GRADILL TEX. DICYDGE, 15

#### DISCLOSURE OF THE INVENTION

QUART (AQUARC 57

5	- In an attempt to develop a method ophnproving the rate of self-disintegration of tablets and at the same timinatural ingular same, the present invertor made investigations concerning the disintegrator species to be used the level of addition the good the binder addition by a province of addition the good the binder addition by a province of addition the good the binder addition by a province of addition to the binder addition by a province of the bi	5
	same, among others and, as a result, the inventor invented β-lactam antibiotic communing table s which are small sized;	
	show good self-disintegrating properties and can be produced by a conventional method.	5.8
10	Furthermore; the inventor found that when granulation is performed using ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol, tablets showing better dispersibility upon self-disintegration can be obtained.	UI
,	The Blactam anthonically sining regimes of this are introduced in pertablet, 50 to 85% by weight of 2 FB lactam anthonical transfer of the same anthonical transfer of the same and the sam	
	have to be considerable large in size, when 400 mg potency raps and bushess priorities on disease, 300mg yotangeni	
15	Preferably the wish with the contain, per tablet 0.5 to 35% byse	₹(
	weight of a synthe and a synthetic and a sy	
	The plactar Contracting States: (72) Invest States characterized that the above-	
	specified respect DE DK ES FI FR GB GR IE IT LI LU NL	
	1941 m. and the state of the st	53
20	the granulation the granulation of the participant of the color of the	
		•
	interticulation 5.507.697 62 ésea ( ) ( ) March 190 enterios 2008. 91. 1, Europh entre	
	upomoratadorina - ) assinta indicides filorescando 1921 - 9 1 Calabi 10595 2006 9 (Conficilidado de Calabia de	
	mulae shown blow as well reside to characterize the control of the	
25	of advanced age or oblidien have a difficulties in swallowing the docage form as such The expression fracid retiriditions.	33
	#@ration" as used herein means that when the preparation is discoped into a class containing a inside each as water	
	the tablet form spontaneously collapses generally within 3 minutes, preferably within 1 moute, so that said or question	
	can be orally taken in dispersion to an without awarting long before raking.	
	It is indeed easy to produce ablets caperale of self-disintegrating very rapidly by incorporating an efferyoscent	
	agent comprising a combination of sodium 1003 carbonate and tarraric acid, tor instance. However, when such table	98
30	lets are graily taken, they give of HOLD the cavito so that panents feel discontible or an unnecessary sense-	
	tion of anxiety. For securing a good shelf-life in a hunid anyironment, it is necessary to use a moisture-proof packaging	
	material, which increases the production cost. They are with the present invention is	
	interrided to provide, it has been a touch probler intended. It has been a touch probler intended to provide, it has been a touch probler intended.	
	intended to provide, it has been a touch problem to provide to provide, it has been a touch problem to provide to provide the second to provide the provide the provide the provide to provide the provi	e."
35		121
	in the form of a dispersion resulting from self-disin' a technology imbaties in European Patent EP	
	(281200 B (corresponding Japanese pages adding 24	
	to 72% by weight, based on the weight of the second of the	
40	this distinguished 2 to 2012 at 16 and 2 to 2012 at 16 and 2012 at 16 at	1/8
	second disingerator.	
	second distinguister.  However said first distinguister and property of the pr	
	tion of a binder component (method in the continuation of Sec. ). See parent fan in the softbiedto, hepceles up stantially nit. This is because the second reference of the se	
	Cocese for producing the trade focusions:	· 87
45	in employed which cold it steems at take of the an which is not considered and not an earlier and indepthy of the arterior in appropriate of the art which is not considered as the considered in a management of the arterior in a property in	
	ANT O II GRIDISHIN DITO PEnns yroun to animare in	٠,
	and the conor of the conor terminal transfer of the conor	
	Wedgittoning of the state of th	
	Total and a construction of the control of the cont	38
50	the about examinating a sequent of hermatical and the sequence of the sequence	
	Durant Market Control of the Control	
	mally Entropy to the correct of the content of the	
	and crosslinke without moved areas at to reduce a member of the property of th	
	energy precion we one the matter of matter of the international sear / repojmentional	٠,
55	2-house a pilot and the series are	
•	be 1000 101 zinkese sidd energlin. mersingsserrens winotablets:	٠
	ion levels and thus suited for abl	

### EP 0 890,359 A1 2 92

The tablets of this invention further ignoration binder as an essential constituent. The addition of a binder has an adverse effect on the self-disintegrating properties of tablets, hence is not desirable from the self-disintegration viewers to point. However, the production of tablets without adding any binder give such inconveniences as mentioned heroinbenesite fore.

The inventor of this invention made investigations in search of binder species which would not give adverse effects on the self-disintegrating properties of tablets as well as investigations concerning the addition level thereof. As preferred binders, there may now be mentioned, for example, polyvinylpyrrolidone, hydroxypropylcellulose, preferably low-viscosity type (L-type) hydroxypropylcellulose, hydroxypropylmethylcellulose; methylcellulose, starch, pregelatinized starch, liguin arabic, dextrin, pullular, and the like. Among these binders, polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylcellulose are more preferred, and polyvinylpyrrolidone is most preferred. When these binders are used in an amount of 0.5 to 2% by weight, preferrably 0.8 to 1.5% Weight, on a personal tablet basis, tablets which can self-disintegrate repidly can be produced by a conventional production method. Onstog pre-

Since β-lactam antibiotics, for example cefixime and cefdinir, have a strongly bitter taste, it is necessary to add at example cefixime and cefdinir, have a strongly bitter taste, it is necessary to add at example synthetic sweetener in cases where tablets are to be taken in the form of dispersions after self-distribution in water, and instance, though this is necessary in cases where tablets are to be taken as such.

As regards the synthetic sweetener addition level, which may vary according to the synthetic sweetener species and the active ingredient β-lactam antibiotic, the sweetener is incorporated in tablets generally in a proportion of 0.5 to 15% by weight, preferably 1 to 10% by weight.

The commercial synthetics westerer products are generally small, i.e. less than 150 µm, in mean particle size, with particle 'not smaller than 150 µm accounting for at most 4% of the whole. Incorporation of scient products markedly reduced the rate of disintegration of tablets. To improve the disintegration rate, the prior art entitions a method which is comprises incorporating a large amount of an excipient such as microcrystalline callulose. However, incorporation of a large amount of scan excipient according to said method results in an increase in tablet size, thereby making the tablets difficult to take with ease. The present inventor found that when the particle size of a synthetic sweetener and light anhydrous silico acid. Indicated silicon distribution or the like is added, the rate of disintegration can be improved, namely prevented from retardation.

As a result, an invention was made of miniaturized tablets which can be easily taken as such and, when dropped into water in a glass, can rapidly self-disintegrate, enabling administration thereof in dispersion form.

When such a synthetic sweetener as saccharin a salt thereof (e.g. saccharin calcium, saccharin sodium), cyclamic acid or a salt thereof (e.g. sodium cyclamate, calcium cyclamate, altimornium cyclamate) is used, said sweetener is required to be not less than 150 µm in mean particle size, preferably not less than 150 µm in particle size. In the case of a sweetener capable of producing a satisfactory bitter masking effect in small amounts, for example aspartame, it is not always necessary that the mean particle size be not less than 150 µm, since the disintegrability of tablets is little affected.

The synthetic sweetener may be incorporated either in the form of crystalline grains having a mean particle size of not less than 150 µm or in the form of a granulation product meeting the particle size requirement as obtained by wet granulation from the powder form small in mean particle size or by wet granulation or dry granulation from such powder together with a color additive and/or microcrystalline cellulose or a like excipient.

The granulation product containing light anhydrous silicic acid or hydrated silicon dioxide in addition to a synthetic sweetener can be produced by mixing the synthetic sweetener with 1 to 30% by weight, relative to the synthetic sweetener weight, of light anhydrous silicic acid or hydrated silicon dioxide and granulating the mixture in the conventional manner, if necessary using a binder and/or one or more observables in common use. It was found that in the case of granulation products containing a synthetic sweetener together with light anhydraus silicic acid or hydrated silicon dioxide, the particle size is not critical, with the result that the self-disintegrating p topical larger adversely affected even when the mean particle size is below 150 µm. As regards other ingred ance micropized producing the tablets of this invention, the same ingredients or additives as used conventionels is pyrrolidone, toped preparations may be mentioned. Thus, in addition to the above-mentioned synthetic swaying under flowing air mailic sweetener, excipients such as microcrystalline cellulose, lactose, mannitol, starch, c. ... ow at annydrous silicic acid, hydrated silicon dioxide, etc., lubricants such as magnessillatearaparticle sub-silicon dioxide, etc., lubricants and lubricants and lubricants are such as magnessillatearaparticle sub-silicon dioxide, etc., lubricants are sub-silicon dioxide, etc., other agents may be incorporated Chiess the self-disintegrating proof les inversely affected. When the β-lactam antibiotic has a large particle size, it may be ground prior to use. In this case, however, wet or dry granulation is required to improve the powder flowability in the step of compression. ressigked pulyvinylpytrolidane

In a preferred process for producing the tablets of the present invention, the acoverspecified disintegrator and billider, optionally together ingredistress are added to the β-lactam antibiotic, the mixture is granulated by a conventional method, the above-mer/long a synthetic sweetener, and/or cranulated synthetic streeten with one or more other ingredients (e.g. flowability improver, lubricant, flavor), are then further additional resulting mixture is subjected to tableting.

When, in the above production process, water is used for granulation in the granulation step, tablets with good self-

### EP 0 890 359 AT

disintegrating properties are generally obtained. In this confrection, the inventor of this invention further found that when ethanol risepropyl alcohol or a mixture of water and ethanol or isopropyl alcohol is used for granulation; tablets with good self-disintegrating properties and with very good dispersibility upon allowing dispersion in water can be obtained. The concentration of the aqueous solution of ethanol or isopropyl alcohol, which is suited for use, is 3 to 99% (vol-The concentration of the enterty made investigations of branch of branch of concentrations of tables as well as investigations concerning the addition of tables as well as investigations concerning the addition of tables as well as investigations concerning the addition of tables. rai red bindera, there may now be mentioned, for axistrale, polytrophore, hydrotypiopyloellilisse, preferably for viscosity type (Lityce) hydroxypropyloeilulose, hydroxypropylmethyloeilulose, met ytoeilulos**ti tyllepi (Lityce) hydroxypropylmethyloeil**ulose, met ytoeilulos**ti tyllepi (Lityce)** The thus obtained & lactam antibiotic containing tablets of this invention are similar dize. For example, a tablet many the thus obtained & lactam antibiotic containing tablets of this invention are similar as tablet containing 300. containing 400 mg potency (about 449 mg) of certxime may wellon not more than 600 mg and a tablet containing 300 nor mg potency (about 307 mg) of certiful not more than 450 mg. They can be craffy taken as such with sace. When they sign are to be taken by the aged, for instance, complaining of some difficulty in swallowing, in an acueous dispersion form, the tablets can be racidly disintegrated and dispersed in water. Moreover, the use of ethanol, isopropyl alcohol or an aqueous solution of ethanol or isopropyl alcohol for granula. Moreover, the use of emanufacturity of the second results of the s Test Example 1 (Disintegrator effect)

Test Example 1 (Disintegrator effect) 15% by weight, preferency 1 to 10% by ive at . we assembly a service of the control of the service of the control disintegratoral light aphydrous silicic acid and magnesium stearate, taken in the respective specified preportions, were each by a paternatic action of a new year and a superior of a new year and the comprises incorporating a large amount of an each year such as microcopy and the celling and th mms dot: general prince of the production of the using a Japanage Pharm Soneja disintegration tester but without using any committee per mit ute of basket using a descending. The distribution can be improved, namely provented from the distribution can be improved, namely provented from the distribution can be improved, namely provented from the distribution can be improved. As a result, an invention was melte of min aturited tablets which can be easily fallen as such and, where if ead water in a glass, orn rapidly self-disintegrata, enabling **r dida**ration thereor in disr<sup>©</sup>igon form. When such a synthetic sweep (¿phērod gm² 004) e 844 er a salt thereo! (e.g. sodium e rolamate, carollum cycl pinaloy: (mulaos rélado said oviesiener is and or a salt thereof (e.g. sodium equires to be not less than 150 Jun in mean particle **9:88** preferredubles smillist yil wcie size in i'u case /nple asparto ne, it is of a sweetener capable of produking a setisfactory bitter analysis efect in small o not always necessary that the meen penisio size be not less than 150 jum, sold. elitil at ablets is little : anhydrous silicic acid The synthetic eve etener melt be incremed **eite e** in the form of crystalina crane and an incrementation of the synthetic eve rmean particle size of tew vid peniatdo ae tr nor less than 150 jum or in the fo granulation from the powder form strell in mean period 888 or by wet granulation or i iion from such cowder regether with a color additive ancier microcrystalling cellulose or a nimexcoperno ulterate is a concertible. The granulation product contening light enhydrous choic acid or hydrated silicof yo the syrthetic sweet gweetener can be produced by mixing the symheric sweetener.with 1 - 30% by weld ener weight, of light arrhyw sus silids arid or hydraled silison dioxide and gressifilis and the con-ent con wase set of theit t manner, if necessary using a sinder analor one of more ou xuib riupilis baissit Disimegration tinie (min.) granulation products o that the self-commograms p activities violated affected inesa ell 변화e copic toc ic alekta edi onbul ggradiei <sup>6</sup>5<sup>1</sup>5<sup>2</sup>edditives a old kişəli subophyandan notine to report 2 if of notine reentioned. Thus, in ac Starch hic antrydrous sitioir iavonii glagęnty and When the Glattain 8000 Jajsnograp Law-substituted / Groxy opyliceliulus3 other **agents m**ay be in behaces at colletions sotiblictic has a large cCrosslinked polyvinylpyrrolidone a tables of the present invection, firin a preferred persess for producing inable which contain now custiful a verexy are py relied containing containing containing vir./perc. no in accom ance with the present invention distintegrate very at Asmesses en control month even

When, in the bowe promitted process. I water is used for granulation in the premulation shap, (set like with mind cart-

cogather with one or errice other ingradients (a. . Fourbilly improved, idbilitation

cashing midure is subjected to minerally

#### Test Example 2 (Binder study)

15

50

According to the formulation shown below in Table 3, cefixime bulk substance micronized by a pin-type mill, microcrystalline cellulose and one of the binders regetter with 50% (by volume) ethanol; were granulated in a high speed shear mixer, followed by drying under flowing air at 40°C for 17 hours and sizing through a 500-µm sieve. The granules sieved out were mixed with low-substituted hydroxypropylicellulose, light anhydrous silicic and and magnesium stearate, in the respective specified proportions, followed by compression on a single-punch tablet machine, to give tablets each having the specified weight and a diameter of 11 mm.

The tablets produced by the above method were evaluated for disintegration time under the same conditions as in Test Example 1. The disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the disintegration time data thus obtained are shown in Jable Anyony in the distinction of the distinctio

Total			538.7 mg (5	48.4 mg)
Magnesium stearate		1.	5.9	
Light anhydrous silicic ac	id .	·*************************************	1.2	
Low-substituted hydroxyg	propylcellu	lose	38.9	1670:
Binder	0.00		4.9 (14.6)	ಆಗಾಗಗಳನ್ನು
Microcrystalline cellulose	•		38,9 <sub>nun'sc</sub>	riberius ?
Cefixime	4,4		.448.9 (400 n	ng potency)
!	e (Table	e 3	etaarate :	nuigembels
		•	note application	skoue iubm

	[ ectato	heigemen mael.A					
	1 8	r W (mpar)				*FP:77	for we premin 3
	}	0.8	Appendix to the annual of the designation of the section of the se	The second second of the second secon	and the same and t	-	
	<u> </u>	1.6.0		Table 4	(mu 631 > esta es	estiment) in	s S consum calcu
		Binder	1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1 (1		(m. 168-03)	¥750) (1	) Sacunarin cator
	;	binder	, 198 (1985) # 5 [	% addition level (v in mg)	Actions of the State of the Sta	`(min:) (\daggerian)	Seconar 1101
:	-	Polyvinylpyrroli		0:9 (4:9)		3	(n <sub>14</sub> )
	arua e indre					* 20,000 + 2000 + 41	or and the first of the second second
, · · · ·	ะการการการ เกาะความเกาะ	Polyvinylpyfroli	idoneo a recisione de	artous: <b>⊝2:7</b> (1 <b>4,6</b> ) <sub>U</sub>	tal ixig ateld(	al oien.	Aşib xiden:
	osia elain	Hydroxypropyl	cellulosé (L type)	0.9 (4.9)	เกล คนไอโรว กกร์		or any granulater
		Hydroxypropyli	methylcellulose	adou :s e <b>2:7/(14,6)</b> ( fis aucro <b>or(s;4:5)</b> ii i o au ninad :	ariog and pold	√ੇ ਨੇ ਣਾਂਜ਼	dat erit alt eine
	•	Little in the viriage	one chart arill until notifi	PRINCIPLE OF GRADIES	การเลือดเก็	3 'stared'	Picigmosi: (##
crys ethating strav Exampres	According stalline cellinol, were purely to the control of the cellinol of the	Internyloeikulosers  prover rebrace  3 (Synthetic swe  50 best receit a  flottle formulatio  flulose, low-subst  grantilafed man  out and  be mentioned lat  xample 2 to be man  inch tablet mach	is the binder disintender of the particle size the same particle size the shown below in the distributed hydroxypropight speed shear migranules sieved or commercial saccher herein or the granetioned later herein or to aive tablets expended.	ced by using polyving egrate rapidly.  study) numbers be as trudy) numbers be as trudy) numbers bull ylcellulose and polyvixer, followed by drut were mixed with liarin calcium, the lainulated mixture of sein, in the respective ach having the spec	an agar	by a pin-ty Juner with 509 at 40°C for 17 ic acid, magnetic accharin calcium ad light anhydrous, followed by tiameter of 11 m	n prepared in a ous silicic acid compressing?
Test	The table Example	ts produced by th 1. The disintegra	e above method wattion time data thus	ere evaluated for dis obtained are shown	integration time un in Table 6.	der the same co	inditions as in
	LAGINDIC	Trine Gion Regid	mon anne data mus	ODIGINIOU GIO SIONI	ini labie o.		,

cars and engineers of a given as a first give naday? Chery detung dropped one 20 milion ware, oracled to 150 or peer or 110 a whole was allowed to exact for 5 min-Clearfor self or Cotagram of Them, the beacher was shaken portly for caming and therepher allowed to staire for Ciminute.

PER RIVER DEPONITOR	and others	Actable 5 for 1.5 Skills	Old Marie	
TO CLES FOR CHARACTER TO	Sept. 62, 2005, 20	SCHOOL SECTION OF THE	28.30 (0.00 (0.00))	٠.

ំ. ផ្ទះ 🕥 👉 រគ្គៈសមត្ថ	<u>िक्षेत्र प्रत्या प्रत्याच्याच्याच्याच्याच्याच्या</u>	448.9 (400 rag potency)	nd to the local content is assetted.
ेक्ट आरम् नार्वे अस्ति ।	Certaine	The Agree of the	nation of a more of the angle of the second
and mayor and owner	binicrockystalline cellulose paciti	bartured typerory reference	iouni. Tui takimisti kii tuo telato
etek i avişinti arifond	Low-substituted	principal distriction of the control of the company	nn puda a kisaku upa sarah bu man sarah sarah man kiyakadan
to Paralingian conside	hydraxypropylsellylose sin to be	Tail 38.9 YEAR DO TON'S YOU	PER LOW COUNT ONE TO
	Polyvinylpymolicone managers	s ba <b>4.9</b> Aloreur section d	agenmanian dell'i din 11 Paell
	Light anhydrous silicic acid	1.2	
	Maguesinui stegiare	3.6.8 <b>5.9</b>	
	Strawberry powder flavor	7.5	meter i
+,	Saccharin calcium or	grand Agentary gentle	Prince to
	granulated saccharin calcium	20.0	e diangraph.
		2558/2 mg > 250 - 34 to 1	we ( )
	5.1	e from the arms a	districts in
	6.5	Sign of the second seco	the section of
	736.7 mg (546.6 mg);	Application of the Control of the Co	The state of the s
•	Taide	16	***

Table 6

Mean disintegration time Synthetic sweetener (min.), n = 63.0 Saccharin calcium (mean particle size < 150 μm) 0.6 Saccharin calcium (particle size 150-840 µm) Saccharin calcium-light anhydrous silicic acid mixture granulated (particle size 75-500 12:4:3 30 1. AA. 20

As is evident from Table 6, the tablets produced by using the saccharin calcium not less than 150 µm in particle size or the granulated mixture of accharin calcium and light anhydrous silicic acid are positively shorter in disintegration time than the tablets produced by using the commercial saccharin calcium smaller than 150 µm in mean particle size.

Test Example 4 (Influence of the composition of the solution for granulation on the dispersibility of tablets)

A 2,200 ml portion of water or an aqueous solution of ethanol was used to granulate a mixture of 4,566 g of cefixime bulk substance micronized by a pin-type mill, 405 g of microcrystalline cellulose, 405 g of low-substituted hydroxypropylcellulose and 50.6 g of polyvinylpyrrolidone in a high speed shear mixer and, after drying under flowing air at 40°C for 17 hours, the granulation product was sized using a 500-µm sieve. The granules sieved out were mixed with 50.6 g of light anhydrous silicic acid, 101.2 g of magnesium stearate, 75.9 g of strawberry powder flavor and 202.6 g of saccharin calcium (particle size: 150-840 jum), followed by compressing on a rotary table; machine to give oblong tabless รั้งกับ<sub>เ</sub>ลิ ซึ่งเลล้าอย่อง หลายเปิด ใน และกฎ (กับ การ) จาก และสมัย พระวิจาย (กับกลาง แต่ยและพระชั่งอ each weighing 579 mg-

ion weigning அது ராழ். ு The tablets produced by the above method were evaluated, by the method mentioned below, for disintegration time as well as for dispersibility for use in dispersion form.

#### Example to be murped for tellor in the content of the saluched realizable and into medical differential and Disintegration time

10

in university **S**uprograding seeks to be programed to the contraction of the contraction The disintegration time evaluation was made in 1,000 ml of water (20 ± 1°C) using a Jaconese Pharmacopeia dis-The disintegration time evaluation was made in the distribution tester, but without using any disc, with 30 cycles per minute of basket ascending and descending integration tester, but without using any disc, with 30 cycles per minute of basket ascending and descending.

### Dispersibility after standing of dispersions prepared

One tablet was dropped into 20 rnl of water placed in a 50-ml beaker and the whole was allowed to stand for 5 minutes for self-disintegration. Then, the beaker was shaken gently for stirring and thereafter allowed to stand for 1 minute,

#### followed by observation of the appearance.

by observation of the appearance.	(Germings) 3 erdet	
ुन्त हैं	Table 7	neric user-trau Stren
6a. 2 ;	Disintegration time (sec.)	Dispersibility after stand-
Granulation using 50% ethanol	39	sta <b>a</b> re a munaang
Granulation using 10% ethanol	(eths albitha <b>84</b> ); min 051 mi	nt exel (cn) raviolat niveb
Granulation using water	62	. brive yrisawi
Flemoxin Solutab 500 (commercial product)	46	b

- a: Wholly uniform in color, substantially without any precipitate.
- b : A supernatant and a slight amount of a precipitate.

À A

The tablets derived from the grapules prepared using ethanol are still better in dispersibility after standing as com-The tablets derived from the granules prepared using water in the control of the same control of the pared with those derived from the granules prepared using water. with balancing errors and rocket facts. It some engreed the procedure and princetot booked are really as a significant of the procedure and the procedure an

Test Example 5 (Disintegration test)

chase, sed in iter of 20 mg is enothern onlothin (Example 1) lable 2. Test preparations A: Tablets produced in Example 1 to be mentioned later. B: Tablets produced in Example 7 to be mentioned later. C: Tablets produced in Example 8 to be mentioned later.

e consequentions and hydrated alticon dicuide wirse nivaritogether in a ratio of 1.14 and then water was and ed Test method Linear praying or or as grant later by a convention main soft of the regulation of the results of t

The disintegration time evaluation was performed in distilled water at 20 ± 1°C with 4 cycles per minute of basket in ascending and descending, using an apparatus prescribed in the Japanese Pharmacopeia (12th edition) under the Tapanese Great, or who manifes to got the use where been and

Disintegration Test.

10

Test results depressed in an informations and of ben idded make entirely, to (yourseq) you (Oh, prodistrion to be stellost har it Heft of Exported (Table 8) was replaced by the name crocura or prosidenced powertylpy collidence (Kellipon Million

- B: 1.30 minutes
- C: 1:02 minutes

A GICTIEST.

The disintegration test results indicate that the test preparations A to C of this invention each shows good disintegrability in accompany to work or the time and the statement of the section of property and another way the contract of the section of the se

#### **EXAMPLE**

ingales i stone of in as ison in amiss which es Water was added to saccharin calcium and the mixture was granulated by a conventional method, followed by drying, sieving and sizing to give saccharin calcium granules not less than 150 µm in particle size. The control sactor is the size of the si

According to the formulation shown below, micronized ceftxime bulk substance, microcrystalline cellulose, low-substituted hydroxypropylcellulose (L-HPC) and polyvinylpyrrolidone were weighed and mixed together, water was then added, and the mixture was granulated. The granulation product was dried under flowing air at 40°C for 17 hours and then sized using a 500-umisieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawborry flavor and the above-mentioned granulated saccharin calcium according to the formulation shown below, followed by compressing on a single-punch tablet machine to give tablets each having the specified weight. and shadd sen, of ECO and evel. The drainules maked on world museum thoughest understand the product and animal areas

Functions. (2) andreses the property of the grant state of states and the grant of the states of the

P 767 6	it on ashers having th	The property of	Table 8 articula botsim	end the cra	Videntia, is the propher
	wicronized cerixim	bulk substanc	.(8)	448.9 mg (400	mg polency)
	Microcrystalline cell	lulose (Avicel™ PH1(	01; Asahi Chemical Industry)	38.9 mg	July July

Table 8 (continued)

birowed av onservation or me aphearance.

Distanceration Test

asuraim 30d till .

L-HPC (LH-21; Shin-Etsu Ch	nemical)	38.9 mg
	( On: ii	4.9 mg
Light anhydrous silicic acid (	n™-30;-BASF) - (∴=a) arre nese getrusi€ Aerosil™; Tomita Seiyaku)	1.2 mg
Magnesium stearate	de la financia communicación de la communicación de la communicación de la communicación de la communicación d Escar	tenerite 1805 phiasi ncitalune O
Saccharin calcium (not less	than 150 µm in particle size)	oned & prize at rate of
Strawberry flavor	16	7.5 mg
Total	1001 1 44	566.2 mg

Example 2

10

15

Saccharin calcium and light anhydrous silicic acid were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mix-

a. Alvolly minternally so in soly as advision and medicine disland. . A supermarkit and it by it amount on a principlinal

membrace large. Col Tables vol. 39 and in Villago a rich entroped leter.

Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8). Districtionpetals(Distance) issued issue

Example 3

Saccharin calcium and hydrated silicon dioxide were mixed together in a ratio of 20:1 and then water was added. The resultant mixture was granulated by a conventional method, followed by drying and sizing to give a granulated mixture ture of saccharin calcium and hydrated silicon dipxide (75-500 µm in particle size).

Tear or epigations: A: Teturant probused in Eulantide it to be mentioned tuted. Et Tablets productable if Eurapia int

Then, tablets were produced following the procedure of Example 1 except that 21 mg of the above granulated mixture was used in lieu of 20 mg of saccharin calcium (Example 1, Table 8).

Example 4

Tablets each centaining 400 mg (potency) of cefixime were produced in the same manner as in Example diaxceptor that L-HPC of Example 1 (Table 8) was replaced by the same amount of crosslinked polyvinylpyrrolidone (Kollidon™ CL; BASF). B: 1.30 minutes

Example 5

Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example bexcept that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylcellulose (HP.Cr.Lip Nippon Soda). F. AWAK-

Example 6

Y Tablets each containing 400 mg (potency) of cefixime were produced in the same manner as in Example 1 except that polyvinylpyrrolidone of Example 1 (Table 8) was replaced by the same amount of hydroxypropylmethylcellulose ் திழு richaled minusches avit of gritch brus galvers .ge According to the commences and a source of colors of the source of the commences of the com

ertuted typic generylicetured (1.146), and colymnycymnicade in in weith a kild a weith

Example 751 - 12 is the grid. While be because on being unablined the formula greater and an entiting before

The surface of the same formulation as that shown in Example 1 (Table 8)? micronized certains bulls substance. microcrystalline cellulose, L-HRC and polyvinylpyrrolidone were weighed and mixed together, 50% aqueous ethanol was added, and the mixture was granulated. The granulation product was dried under flowing air at 4010 feet 17 bours. and then sized using a 500-µm sieve. The granules sieved out were mixed with magnesium stearate, light anhydrous silicic acid, strawberry flavor and the granulated saccharing alcium prepared in Example 1 (not less than 150 µm in perticle size) and the regultant mixture was compressed on a single-punch tablet machine to give tablets having the same

composition as that in Example 1 (Table 8). factocrysialine calulose (Alicelin PH 271, leath Chemical Industry) |

#### Example 8

	nple 7	PCT/:281.00809				
				UELIKT MATTE	· · · · ·	
	. 1		9736; 364447/1 <b>9 alds</b> T		and the second	
	- 1	Micronized cefdinir bulk substance	ार राज्य व्याज्यक वीक्सार		O mg-potency)	at Solition
	-	Microcrystalline cellulose (Avicel Per	ollowed by the servanople		market a mark in Charles and a contract of	າ ວ່າ ເຫລ
		L-HPC (LH-21)	9/20, ASLEST /	X 13 / 3 4 2 \ / 29.2 mg	Extra Astixa	
,	-	Polyvinylayrsolideme (Kellidon Sa)	oo dage ton outre an all ar	a Landaria Sa Tangar ar	ing and the control of the control o	and the second
	. :	Light anhydrous silicic acid (Aerosil)		0.9 mg		
		Magnesium stearate	ren france of hazz base that		Commence (in the commence of t	-
		Saccharin calcium (not less than 150		15.0 mg		
			min in bandore area			
		Strawberry flavor	Tale a	5.6 mg	ELOTISMON STEEN	,
	<u> </u>	Total	Company of the Compan	TESSE Miga	* ************************************	F
	<u></u>	AND THE PROPERTY OF THE PARTY O	. where apprepriate, or the		page, legislis administration from transfer	درود. در محدد الجد
air	ns		-Brodedes N.V.	20, A (Gist		
	1	The Aller & Bent	eft column.	.oug batti Laewal C	. A TACKET BU	
t	o 2% by A tablet	s claimed in Claim 1, wherein the bind	paça C. Eppor st left tolum	୍ଚିପ୍ଟିଲିଅନ ଜଣ ଓଡ଼ିଆ	nid (nmale) nid (amalo)	
t	o 2% by	weight of a binder per tablet.	paça C. Eppor st left tolum	one, hydroxyproj	nii i na i na nii i na i na pylcellylose or ny	droxyp
t	o 2% by A tablet methylce A tablet	weight of a binder per tablet.	page 6. uppekt st. left column pilonnydygiyylog af el unpkredt I.co.: Not 2.0°ææinamone	one. hydroxyproj	o i i o o o o o o o o o o o o o o o o o	droxyr
t r	o 2% by A tablet methylce A tablet a granuli	weight of a binder per tablet.	page 6, uppeld in ledt redum bloggydygiydpigelid angleget I ac Tol 2.0 æesingmon re di rootuun, i	one hydroxyproj stanta one hydroxyproj stanta stanta stanta stanta one stanta one stanta	nii naulo nii naulo gylcellulose or fy 1011-00 st a synthetic swee en eq unicalo 1911 depen	droxyr
t r	o 2% by A tablet a methylce A tablet a granula	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.	page 6. uppekt in laft vertum ler is polyvigylpygyld in agkrede. The hot 2.0 æeinqmen dir oolutar, i lum, isne 8	one Tyckoxyproi	nii nm. i o nii nm. i o pylcellylose or in i nii - Ca a synthetic swee e neg nm. i su ggu a ppeg	droxyr tener (
t	o 2% by A tablet a methylce A tablet a granula	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.	page 6. uppekt in laft vertum ler is polyvigylpygyld in agkrede. The hot 2.0 æeinqmen dir oolutar, i lum, isne 8	one Tyckoxyproi	nii nm. i o nii nm. i o pylcellylose or in i nii - Ca a synthetic swee e neg nm. i su ggu a ppeg	droxyr tener (
t r e	o 2% by A tablet a Methylce A tablet a granula A tablet coarticle	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthize of not less than 150 gm.	page 6, uppel.  10 10 10 10 10 10 10 10 10 10 10 10 10 1	one. Tygłoxyproj	niii nmulion nii n	droxyr tener a
t i	o 2% by A tablet a methylos A tablet a granula A tablet a particle s A tablet	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthesize of not less than 150 gm.  Is claimed in Claim 4, wherein the synthesize of not less than 150 gm.	page 6, uppel.  10 10 10 10 10 10 10 10 10 10 10 10 10 1	one Tygloxyproj	nition name to a control of the cont	droxyr tener i nas an
t	o 2% by A tablet a methylos A tablet a granula A tablet a particle s A tablet	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthize of not less than 150 µm.  Is claimed in Claim 4, wherein the synthia claimed in Claim 4.	page 6. uppel.  10. Let con university to 15  10. Top 2. Top 2. Top 2. Top 3. T	one, hydroxyproj	niii nm. i no nii nm. i no nylcellulose or in i nii ne nii a synthetic swee e p s q nii s u n e p s q nii sweetener l nii nii sweetener l	droxyp tener : has an
t in the second	o 2% by A tablet a methylos A tablet a granula A tablet coarticle A tablet A tablet A tablet A tablet	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further that synthetic sweetener.  Is claimed in Claim 3, wherein the synthesize of not less than 150 µm.  Is claimed in Claim 4, wherein the synthesize of not less than 150 µm.  Is claimed in Claim 4, wherein the synthesize of the synthes	thetic sweetenar.or thetic sweetenar.or the same same same same same same same sam	one. Toyaloxyproj	niii namul oo nii namul oo nylcellilose or iy la in oo get a synthetic swee e ped nais ii ngu oo ged netic sweetener!	droxyp tener a nas an
t / r / s / r / t / r / r	o 2% by A tablet a methylce A tablet a granula A tablet A tablet A tablet ight anh	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ited synthetic sweetener.  Is claimed in Claim 3, wherein the synthesis claimed in Claim 4, wherein the synthesis claimed in Claim 4, wherein the synthesis claimed in Claim 3, wherein the synthesis claimed in Claim 3, wherein the grand or claim 3, wherein the synthesis are claimed in Claim 3, wherein the grand or claimed in Claim 3, wherein the grand or claimed in Claim 3, wherein the grand or claimed in Claimed	popular de la contraction de l	one hydroxyproj	niii nm. i on ii o	droxyp tener a nas an er is no
t / r / s / r / t / r / r	o 2% by A tablet a granula A tablet a particle to A tablet han 150 A tablet ight anh	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic of not less than 150 µm.  Is claimed in Claim 4, wherein the synthetic size.  Is claimed in Claim 3, wherein the grand or claimed in Claim 3, wherein the synthetic state of the claim 3, wherein the synthetic state of the claim 3, wherein the synthetic state of the claim 4, wherein the synthetic state of	er is polyvigylpygrolid  op I abouter  er comprises 0.5 to 1  er com	one hydroxyproj	niii nm. i on ii o	droxyp stener a nas an er is no eetene
t ii	o 2% by A tablet a granula A tablet a stablet A tablet han 150 A tablet tight anh	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 4, wherein the synthetic strain 150 gm.  Is claimed in Claim 3, wherein the synthetic strain in particle size.  Is claimed in Claim 3, wherein the grand on the synthetic strain in the synthetic strain	ler is polyvinylpyrrolid  er is polyvinylpyrrolid  er comprises 0.5 to 1  er comprises 0.5	one. Typicxyproj	ntil and local control of the contro	droxyp tener a nas an er is no
t / r / s / r / t / t / ii	o 2% by A tablet a granula A tablet a particle to A tablet han 150 A tablet and A tablet and A tablet and A tablet and	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 4, wherein the synthetic strain of the synthetic strain in particle size.  Is claimed in Claim 3, wherein the grand or sall in the synthetic strain in particle size.  Is claimed in Claim 3, wherein the grand or sall in the synthetic strain in the sy	ler is polyvigylpyrrolider is polyvigylpyrrolider is polyvigylpyrrolider is polyvigylpyrrolider is polyvigylpyrrolider in the comprises 0.5 for the comprise of the compr	one. Typicxyproj	a synthetic sweetener line is a synthetic sweetener line is sweetener line is a synthetic sweete	droxyp
t	A tablet a granula A tablet a particle to A tablet a particle to A tablet a particle to A tablet a tab	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind llulose.  Is claimed in Claim 1 or 2 which further ted synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 4, wherein the synthetic strain 150 µm.  Is claimed in Claim 4, wherein the synthetic size.  Is claimed in Claim 3, wherein the synthetic size in the synthetic size in the synthetic synthetic size.  Is claimed in Claim 3, wherein the grand control of the synthetic synth	ler is polyvinylpyrrolid  er comprises 0.5 for the second of the second	one. Typicxyproj	a synthetic sweetener line is a synthetic sweetener line is sweetener line is a synthetic sweete	droxyp tener a nas an eetene greate
t / r / r / r / r / r / r / r / r / r /	A tablet a granuli A tablet a particle to han 150 A tablet a channel A tablet a tabl	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ited synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic of not less than 150 µm.  Is claimed in Claim 4, wherein the synthetic size.  It is claimed in Claim 3, wherein the grandrous silicic acid and/or hydrated silic and and or hydrated silic and and acid the synthetic size.  Is claimed in Claim 3, wherein the grandrous silicic acid and/or hydrated silic and and acid the synthetic size in the synthetic siz	ler is polyvigylpytrolid  on I should an arrival and a should a shou	one hydioxyproj	a synthetic sweetener in the tic sweetener in the t	droxyp tener a nas an eetene
t i i i i i i i i i i i i i i i i i i i	A tablet a granuli A tablet a particle to han 150 A tablet a channel A tablet a tabl	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ited synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 4, wherein the synthetic standard in the	ler is polyvigylpytrolid er is polyvigylpytrolid er comprises 0.5 to 1 er comprises 0.5	one hydioxyproj  5% by weight of  granulated synt  if granulated synt  biroic is certaine  biroic is certaine  dhis, the tablet	a synthetic sweetener in the tic sweetener in the t	droxyp tener a tener a nas an er is no
t in the second	A tablet a granular A tablet a granular A tablet a granular A tablet a carticle a A tablet a datablet a tablet	weight of a binder per tablet.  Is claimed in Claim 1, wherein the bind illulose.  Is claimed in Claim 1 or 2 which further ited synthetic sweetener.  Is claimed in Claim 3, wherein the synthetic synthetic sweetener.  Is claimed in Claim 4, wherein the synthetic of not less than 150 µm.  Is claimed in Claim 4, wherein the synthetic size.  Is claimed in Claim 3, wherein the grandrous silicic acid and/or hydrated silicing and an acid and/or hydrated silicing and acid and/or hydrated silicing and acid and/or hydrated silicing acid and/or hydrated silicing acid and/or hydrated silicing acid and/or hydrated silicing acid and acid and/or hydrated silicing acid and acid and acid and acid acid acid acid acid acid acid aci	ier is polyvinylpyrrolid  or I abouter  er comprises 0.5 to 1  a abouter  hetic sweetener or the  isolated synthetic sweetener  nulated synthetic sweetener  on dioxide.  seein the β-lactam and  on dioxide.  seein the β-lactam and  on dioxide.  seein the β-lactam and  on dioxide.	one hydroxyproj	a synthetic sweetener hetic sw	droxyp tener a nas an er is no

TO BOOK BOOK AND SECOND

	STATEL NATIONAL SEARCH LEE C	Mariauonar	application No.	3005
•		PCT	/JP97/00509	र्वे क्षांत्र स्थापी । । इ. क्षांत्र स्थापी
Int.	SSIFICATION OF SUBJECT MATTER  C16 A61K31/545, A61K9/20	Davie	38	
cording t	to International Patent Classification (IPC) or to bot  DS SEARCHED (Co.) OF 8 2006	90/1999UC AN	म दिवाद Colved अवस्तर व	
inimum de Int.	ocumentation alarched (classification system followed to C16 A61K31/545, A61K9/20	, A61K47/30, A61K47/	(138 (15-HJ) (19h-J)	
	tion searched other than minigum documentation to the	(Leone * m. ) v t	adio se varrus silica	
ectronic d	have been consulted during the Eternational search (name grow 0.07 (e.s.ia.)	e of data base and, where practicable, sea eloimate calmus (18) 112, 111 /1886 / 19	1	
	5.6 mg		Strawberry haver	
DOC	UNIENTS CONSIDERED TO . LEVANT	regional according to the production of the second of the	tato	<b>.</b>
tegory*	Citation of document, with indication, where	appropriate, of the relevant passages	Relevant to claim No.	
Y Stor co	JP, 63-301820, A (Gist-Bro December 8, 1988 (08. 12. Claim; page 2, lower left page 14, where 1 in 16 scolumn, hower left real union kine 1; column, lines 1 to 4; page	88), column, lines 2 to ( calinesal@ato cuge is apagonis alower righ)	gan listacit loitotitata mat Rabed cetul-teotic-wellic	Tipest.
. <b>Y</b>	column, line 8 to lower le example 3 to 10, 12 to 19, 36 to 38, 41 x EP, 281200,	eft column, line 6; 21 to 25, 27 to 34 Control of the columns of t	i diellum bemisio se i econilec 1 – 10	ider A. S. ( Intern
	Claim; page 5, lower left page 6, upper left column, EEP, 130683, A1 & US, 460	(35km) noo medal doma (1 m column, line 5 to m , line 8 0.579 A 2.584 o medanya edinerah	neted synthetic sventer. Las claimad in C'atm 5, w	rangir Sambalan da Sambalan da
Y on a	JP, 7-324101, A (Shin-Etsu The), December 12, 51995 (12. 120 Claim; page 2, right column page 3, lower left column	re95%, onerwys art mesarw mn. lines 7 to 13;	í	e Jack A lab
Trad	her documents are fister in the continuation of Box		Lis mielū ni bargialaise I	F. Atable
Special documents to be of documents of the documents of	al categories of cited documents:  neat defining the general state of the art which is not consider of perticular felovations of the art which is not consider of document but published on or after the international filling of neat which may throw doubts on priority claim(s) or which to establish the publication date of the or cities of which in establish the publication date of the or cities of which is restored as specified) neat referring to an oral disclosure, use, exhibition or of	later document published after the date and not in conflict with the principle or theory nederly solderly and considered novel or cannot be also when the document of particular relevant the document is taken the document of particular relevant the document of particular relevant to involve an law considered to involve an law considered to involve an law considered with one of more other days.	be international filing date or priority application but cited to understanding the investion of the claims of the considered of involves a investion of the claims of involves an investion of the claims of the combination of the	a /tst A - /3' a /tst A - /3' a /tst A - /8' a / 038
the pr	most probleted prior to the interpretoral (fling date but traced riorly date claimed)  e actual completion of the international search  y_6, 1997 (06. 05. 97.)	Date of mailing of the internation	patest (finity of the mail) 3.9	450 174
	wailing address of the ISA/ itselfine as telbric of	A Company of the Comp	وسيعو بالمتار والمتاريخ والمتاريخ	⇒pahmei

EP 0 890 359 A1 CH ROLLWEZATTON

C MPRINCATION PURESHHO UNIMP THE CORPRATION TREMTY OFFICE

WO SHUSTES : O normal trained " : woodance and the INTERNATIONAL SEARCH REPORT International application No. (2010 9 मिस एक्ष कि वे (वेद के) 653' luces antiqual Publication Detect PCT/JP97/00509 C (Continuation). 4. DOCUMENTS CONSIDERED TO BE RELEVANT 38 3A greedement andapillerst, isani Citation of document, with indication, where appropriate, of the relevant passages Category Relevant to claim No. column, line 2 (Family: none) Y JP, 6-183964, A (Tanabe Selyaku Co., Ltd.) 1 - 10260 July 5 1994 (05:07.94), Claim; page 2; left column, line 35 to right column, Trne 20; page 3, left column, lines 20 to 25 (Family: none) ്**രാന്ദ്യ**്ഗ cersof in receipt of 18 1 W V S Playes 10 (715) 018. JP, 58-109419, A (Beecham Group Ltd.)

June 29, 1983 (29. 06. 83),

Claim; page 2, upper right column, line 4 & EP, 80852 (A1) (887. 1) | Local Mark (Beecham Group Ltd.)

Local Mark (Beecham Group L JP, 50-140623, A (Shin-Etsu Chemical Co., Ltd., 1 - 10 November 11, 1975 (11. 11. 75), it is (20) 02070 11 and a cold of the Claim; page 2, upper left column, line 16 to page 3, upper right column, line 19 & US, 4017598, A "General Techniques for New Pharmaceutical Preparation Development Systems - Bases and Filling Material (in Japanese) " edited by Sadao Iguchi, R & D Planning, July 12, 1985 (12. 07. 85), p. 417-418, 432,436 Old DA YOPELIA LIOU TVEDZBYZETE DYJEKAT THAZZET · relaff 住私 "Drug Handbook (in Japanese) 5th edition" TO Abstract Edited by Osaka-fu Hospital Pharmacists Assoc., A planta testing, extenses a condition gy mer in the growing as a sold at a case and additional and a case and a case and case are extenses as maked using a real field with the case and case acceptance of extenses as maked using a real field with the field of the field of the field of the mount yet privides a big degree of ser broavailability we RESTERE the after conditions with a mount of the mount of the conditions with the conditions with the conditions with the conditions of the conditions with the condition of the conditions with the conditions with the conditions with the conditions of the conditions are conditionally as the conditions with the conditions of the conditions are conditionally as the conditional conditions are conditionally as the conditions are conditionally as the conditional conditions are conditionally as the conditional conditions are conditionally as the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the conditional conditions are conditionally as the condition of the conditional conditions are conditionally as the condition of the co

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

DOCOD WITH BESTERNE